# Common Drug Review
## *Pharmacoeconomic Review Report*

**December 2016**

| | |
|---|---|
| **Drug** | Entyvio (vedolizumab) |
| **Indication** | Treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a tumour necrosis factor-alpha antagonist; or have had an inadequate response, intolerance, or demonstrated dependence on corticosteroids |
| **Reimbursement request** | As per indication |
| **Dosage form** | 300 mg per vial for intravenous infusion |
| **NOC date** | 2016-03-22 |
| **Manufacturer** | Takeda Canada Inc. |

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in gastroenterology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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# ABBREVIATIONS

| | |
|---|---|
| **CDAI** | Crohn's Disease Activity Index |
| **CDR** | CADTH Common Drug Review |
| **IDC** | indirect treatment comparison |
| **NICE** | National Institute for Health and Care Excellence |
| **ODB** | Ontario Drug Benefit Formulary |
| **PBAC** | Pharmaceutical Benefit Advisory Committee |
| **SEB** | subsequent entry biologic |
| **TNF** | tumour necrosis factor |

# SUMMARY

## Background

Vedolizumab (Entyvio) is an integrin receptor antagonist indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a tumour necrosis factor (TNF) alpha antagonist; or who have had an inadequate response or intolerance to or have demonstrated dependence on corticosteroids. The manufacturer is requesting reimbursement in line with this indication. Vedolizumab was previously reviewed by CADTH Common Drug Review (CDR) for the treatment of ulcerative colitis.[1] The CADTH Canadian Drug Expert Committee recommended that vedolizumab be reimbursed for ulcerative colitis, with the condition of price reduction. The price of vedolizumab for the ulcerative colitis submission is the same as the current price submitted for Crohn's disease.

Vedolizumab is available in 300 mg/20 mL vials for intravenous infusion at the current market price of $3,290 per vial. The recommended dosing of vedolizumab for Crohn's disease is 300 mg at 0, 2, and 6 weeks followed by every eight weeks thereafter;[2] thus, the cost of approved-dose vedolizumab is $26,320 per patient in the first year and an average of $21,458 per patient in subsequent years.

## Summary of the economic analysis submitted by the manufacturer

The manufacturer submitted a cost comparison of vedolizumab to branded infliximab (Remicade) and adalimumab (Humira) in the indicated population. The perspective was that of a public drug payer with a time horizon of two years to incorporate both the induction and maintenance phases of the comparators. The assumption of clinical similarity was based on a manufacturer-funded indirect treatment comparison. Only drug costs were considered, all other health care costs having been assumed to be equal for the different comparators. Costs for infliximab and adalimumab were derived using the Ontario Drug Benefit (ODB) Formulary Exceptional Access Program, while the cost of vedolizumab was derived using the manufacturer's current market price. Proportions of patients using standard versus escalated doses of infliximab and adalimumab in the base case with the addition of vedolizumab in a sensitivity analysis were derived from the ACCENT I,[3,4] CLASSIC II,[5] and GEMINI II[6,7] trials, respectively.

The manufacturer reported that treatment with approved-dose vedolizumab ($25,571 per patient in year 1 and $21,458 per patient in year 2) would cost $790 and $6,704 less than the dose-weighted cost estimates for adalimumab ($26,361 and $28,162 per patient in years 1 and 2, respectively) and $7,394 and $10,490 less than the dose-weighted cost estimates for branded infliximab ($32,965 and $31,948 per patient in years 1 and 2, respectively) (see Table 4 and Table 5).

## Key Limitations

### Uncertainty in the assumption of clinical similarity

No head-to-head trials exist comparing vedolizumab to infliximab or adalimumab for the treatment of patients with Crohn's disease. The manufacturer submitted indirect treatment comparisons using the Bucher method to compare vedolizumab 300 mg every eight weeks after induction to infliximab 5 mg/kg every eight weeks after induction and to adalimumab 40 mg every two weeks after induction, with placebo as the common comparator in each case. The manufacturer concluded that vedolizumab was noninferior to adalimumab for inducing and maintaining clinical remission (where remission was defined

as having a Crohn's Disease Activity Index [CDAI] ≤ 150), corticosteroid-free clinical remission, and inducing clinical response (reduction in CDAI of ≥ 70) and was noninferior to infliximab for inducing and maintaining clinical remission. However, vedolizumab was not noninferior to adalimumab for maintaining enhanced clinical response (reduction in CDAI ≥ 100) and clinical response and not noninferior to infliximab for inducing and maintaining clinical response. The manufacturer did not pre-specify noninferiority margins nor consider the required statistical power. Additionally, there was substantial heterogeneity in study and patient characteristics in the included studies, particularly regarding the proportion of patients who had previously failed treatment with a TNF alpha inhibitor. Similarly, there was considerable heterogeneity in the included studies of three network meta-analyses identified by CDR reviewers comparing vedolizumab to infliximab and adalimumab, with several outcomes appearing significantly different between comparators. Overall, there is considerable uncertainty associated with the assumption of clinical similarity among treatments (see CDR Clinical Report Appendix 6 and Appendix 7), which could not be examined based on the cost comparison submitted.

**Availability of subsequent entry biologic infliximab**

Inflectra, a subsequent entry biologic (SEB) infliximab, is substantially less expensive than branded infliximab. SEB infliximab recently received a Notice of Compliance from Health Canada for the treatment of adult patients with Crohn's disease similar to that of branded infliximab.[8,9] Should public drug plans reimburse SEB infliximab, it would be considerably less expensive than vedolizumab under all reasonable dose-escalation assumptions. SEB infliximab was included in CDR reanalyses.

**Patients escalating to higher-dose regimens**

There is variability in the relative cost of vedolizumab based on the range of doses that may be used for each comparator. The manufacturer estimated the proportion of patients using each treatment who would escalate to higher-dose regimens based on data from the ACCENT I (infliximab),[3,4] CLASSIC II (adalimumab),[5] and GEMINI II (vedolizumab; applied for the sensitivity analysis only — it was assumed that no patient experienced dose escalation in the manufacturer base case for vedolizumab as opposed to comparators)[6,7] trials. These data are not, however, comparable, due to differences in patient characteristics, escalation criteria, study design, and level of reporting detail between trials. As applied to the manufacturer base case, CDR considered it was inappropriate to assume that the absence of recommended escalation for vedolizumab implies it is equally effective to proportionally weighted average doses combining patients using both standard and escalated doses of either infliximab or adalimumab. The manufacturer's submitted indirect treatment comparison justifying the use of a cost comparison was conducted using standard-dose trial data for each comparator (see CDR Clinical Report, Appendix 6).

In a sensitivity analysis, the manufacturer assumed that 47.2% of vedolizumab patients received a single additional dose at week 10 before returning to dosing every eight weeks. This is not aligned with the GEMINI II trial, which reported that 47.2% of patients had not responded at week 6 to vedolizumab induction and were provided vedolizumab every four weeks thereafter.[6,7]

## Issues for Consideration

**Infusion administration costs**

The administration costs of biologic products for the treatment of Crohn's disease in Canada are currently borne by the manufacturer. Should this change in future, subcutaneous injections as well as less frequent infusion schedules, faster infusing times, or both may become relatively more attractive from a cost perspective.

**Dose escalation of vedolizumab**

CDR's clinical expert considered it highly likely that patients using vedolizumab who experienced a secondary loss of response (i.e., initially responded but then worsened) would be escalated to higher doses of vedolizumab as is current clinical practice with adalimumab and infliximab. A maintenance dose of 300 mg vedolizumab every four weeks was included in the GEMINI II trial,[6,7] although doses higher than the approved 300 mg every eight weeks were not included in the product monograph.[2]

## Results and Conclusions

In CDR's reanalysis, at the submitted price of $3,290 per 300 mg vial, and at the approved dose of vedolizumab and standard doses of the comparators, the cost of branded infliximab ($31,602 per patient) is $5,282 (20%) more than the cost of vedolizumab ($26,320 per patient); adalimumab ($22,211 per patient) is $4,109 (16%) less than vedolizumab; and SEB infliximab ($16,800 per patient) is $9,520 (36%) less than vedolizumab when comparator drug costs are based on the ODB Formulary Exceptional Access Program list prices. In subsequent years, the cost of branded infliximab ($25,765 per patient) is $4,306 (20%) more than the cost of vedolizumab ($21,458 per patient); adalimumab ($19,315 per patient) is $2,143 (10%) less than vedolizumab; and SEB infliximab ($13,697 per patient) is $7,762 (36%) less than vedolizumab. There is, however, considerable uncertainty in the clinical similarity between vedolizumab and infliximab or adalimumab for this patient population.

## Cost Comparison Table

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are from the ODB Formulary Exceptional Access Program (July 2016), unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

**TABLE 1: COST COMPARISON TABLE OF BIOLOGICS FOR THE TREATMENT OF CROHN'S DISEASE**

| Drug/Comparator | Strength | Dosage Form | Price | Recommended Dose[a] | Drug Cost in Year 1 | Average Drug Cost Subsequent Years |
|---|---|---|---|---|---|---|
| **Vedolizumab (Entyvio)** | **300 mg** | **Vial for IV infusion** | **$3,290.00[b]** | **300 mg at weeks 0, 2, and 6, followed by every 8 weeks thereafter** | **$26,320** | **$21,458** |
| **TNF Alpha Inhibitors** | | | | | | |
| Adalimumab (Humira) | 40 mg | Pen for SC injection | 740.36 | 160 mg week 0, 80 mg week 2, 40 mg week 4 and every 2 weeks thereafter | $22,211 | $19,315 |
| Infliximab (Remicade) | 100 mg | Vial for IV infusion | $987.56 | 5 mg/kg at weeks 0, 2, and 6, then every 8 weeks thereafter<br><br>May be increased to 10 mg/kg every 8 weeks in patients who have lost response | $31,602 to $46,415 | $25,765 to $,45,088 |
| Infliximab (Inflectra) | 100 mg | Vial for IV infusion | $$525.00[c] | 5 mg/kg at weeks 0, 2, and 6, then every 8 weeks thereafter<br><br>May be increased to 10 mg/kg every 8 weeks in patients who have lost response | $16,800 to $24,675 | $13,697 to $23,970 |

IV = intravenous; ODB = Ontario Drug Benefit; SC = subcutaneous; TNF alpha = tumour necrosis factor alpha.
Note: All prices are from the ODB Formulary Exceptional Access Program (July 2016) unless otherwise indicated.
[a] Based on doses recommended in the appropriate product monographs.[2,8-10]
[b] Manufacturer's submitted and current market price.
[c] ODB Formulary list price.

# APPENDIX 1: OTHER HEALTH TECHNOLOGY ASSESSMENT ORGANIZATION RECOMMENDATIONS

The Expert Review Group of the UK's National Institute for Health and Care Excellence (NICE) published its technical appraisal guidance on the reimbursement of vedolizumab for Crohn's disease by the National Health Service.[11] The Expert Review Group recommended that vedolizumab be an option for treating moderately to severely active Crohn's disease only if a tumour necrosis factor (TNF) alpha inhibitor had failed (inadequate response or lost response) or the patient was unable to tolerate a TNF alpha inhibitor or a TNF alpha inhibitor was contraindicated. Other stipulations included a discounted price agreed to in a patient access scheme and that the need for vedolizumab should be reassessed at least every 12 months and stopped if there is insufficient evidence of ongoing clinical benefit.

The Expert Review Group's recommendation was made on the basis of clinical evidence from the GEMINI trials as well as several cost-utility analyses. The Group concluded that vedolizumab was not cost-effective compared with TNF alpha inhibitors for patients with moderately to severely active Crohn's who had not had a TNF alpha inhibitor before. However, the Expert Review Group concluded that the use of vedolizumab in a population who had failed therapy with a TNF alpha resulted in an incremental cost-effectiveness ratio of £21,600 per quality-adjusted life-year gained compared with conventional non-biologic therapy (equivalent to CAD$44,500 on August 26, 2015,[12] the date of publication for the NICE guidance) when considering the confidential discount from the reimbursement price agreed to in the patient access scheme.

The Scottish Medical Consortium also recommended the reimbursement of vedolizumab for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a TNF alpha inhibitor provided that the agreed-upon patient access scheme providing a discount to the cost of vedolizumab remains available and that patients are reassessed every 12 months to ensure continuing clinical benefit.[13] This decision was also made based on the results of cost-utility assessments.

In contrast, the Pharmaceutical Benefit Advisory Committee (PBAC) of Australia's Pharmaceutical Benefits Scheme recommended that vedolizumab be reimbursed as Authority Required under their Highly Specialized Drug Program similarly to adalimumab and infliximab for the treatment of patients with moderate to severe Crohn's disease following inadequate response to standard systemic immunosuppressive therapy, with further restriction details to be finalized at a later time.[14] The PBAC did not consider the claim of noninferiority to infliximab or adalimumab to be supported, but despite this was satisfied that vedolizumab, on balance, was a reasonable alternative to infliximab and adalimumab. Of note, the PBAC considered the net (incremental) cost of treating a patient with adalimumab, infliximab, or vedolizumab to be nil using confidential special pricing agreements for all three comparators.

Of further note, the PBAC considered the equally effective doses between comparators to be their standard dosing schedules:

- Vedolizumab: 300 mg administered at weeks 0, 2, and 6 and then every eight weeks thereafter
- Infliximab: 5 mg/kg administered at weeks 0, 2, and 6 and then every eight weeks thereafter
- Adalimumab: 160 mg at week 0, 80 mg at week 2, and 40 mg at week 4 and every two weeks thereafter.

# APPENDIX 2: REVIEWER WORKSHEETS

**TABLE 2: SUMMARY OF MANUFACTURER'S SUBMISSION**

| | |
|---|---|
| **Drug Product** | Vedolizumab (Entyvio) |
| **Treatment** | Vedolizumab<br>• Induction: 300 mg at weeks 0,2, and 6<br>• Maintenance: 300 mg at week 14 and every 8 weeks thereafter<br>• Optional 300 mg dose at week 10 if initial response is delayed |
| **Comparator(s)** | Infliximab (Remicade)<br>• Induction: 5 mg/kg at weeks 0, 2, and 6<br>• Maintenance: 5 mg/kg at week 14 and every 8 weeks thereafter<br>• Optional increase to 10 mg/kg every 8 weeks during maintenance<br>Adalimumab (Humira)<br>• Induction: 160 mg over 1 to 2 days week 0 and 80 mg week 2<br>• Maintenance: 40 mg every other week thereafter<br>• Optional increase to 40 mg weekly during maintenance |
| **Study Question** | Unspecified, but consistent with:<br>What are the costs and incremental costs in years 1 and 2 of treatment with vedolizumab compared with infliximab and adalimumab in adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a TNF alpha antagonist; or who have inadequate response or intolerance to or have demonstrated dependence on corticosteroids? |
| **Type of Economic Evaluation** | Cost-minimization |
| **Target Population** | Adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a TNF alpha antagonist; or who have inadequate response or intolerance to or have demonstrated dependence on corticosteroids |
| **Perspective** | Canadian public payer (Ontario as reference) |
| **Outcome(s) Considered** | Total costs, incremental costs |
| **Key Data Sources** | |
| **Cost** | Ontario Drug Benefit Formulary Exceptional Access Program for adalimumab and infliximab, Takeda Canada for vedolizumab |
| **Clinical Efficacy** | Indirect treatment comparisons between:<br>• Vedolizumab (GEMINI II and III) and infliximab (ACCENT I and T16)<br>• Vedolizumab (GEMINI II and III) and adalimumab (CLASSIC I, GAIN, CHARM, Watanabe) |
| **Harms** | Indirect treatment comparisons between:<br>• Vedolizumab (GEMINI II) and infliximab (ACCENT I)<br>• Vedolizumab (GEMINI II and III) and adalimumab (CLASSIC II, CHARM, Watanabe) |
| **Proportion of Patients Escalating Dose** | Vedolizumab: base case 0%; from GEMINI II for the sensitivity analysis (47.2% get extra dose at week 10)<br>Infliximab: ACCENT I (base case: 32% get 10 mg/kg every 8 weeks)<br>Adalimumab: CLASSIC II (base case: 45.8% get 40 mg weekly) |

| | |
|---|---|
| **Time Horizon** | 2 years, induction year and maintenance year; no discount was applied to the second year of costs |
| **Results for Base Case** | Over 2 years, assuming the base case proportions of patients requiring dose escalation and no discount is applied, the manufacturer reported that vedolizumab would cost $47,029 per patient, which was $17,884 less than the cost of Remicade-brand infliximab ($64,913) and $7,494 less than adalimumab ($54,523) |

TNF alpha = tumour necrosis factor alpha.

## 1. Manufacturer's Results

The manufacturer presented a cost analysis comparing treatment with vedolizumab to treatment with branded infliximab (Remicade) or adalimumab (Humira) in adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a TNF alpha antagonist; or who have inadequate response or intolerance to or have demonstrated dependence on corticosteroids. The perspective was that of a public drug plan, with a time horizon of two years in order to include both the initiation and maintenance phases of treatment. No discount was applied in the second year.

The cost comparison considered only drug costs, all other health care costs having been assumed to be equal for the different comparators. Drug unit costs were taken from Ontario Drug Benefit (ODB) Formulary Exceptional Access Program (EAP) list prices for infliximab and adalimumab, while vedolizumab costs were based on the submitted and current market prices. For year 1 of the analysis, the number of units was calculated by dividing the number of days per year (365.25) by seven days per week, then subtracting the number of weeks in the induction phase (14 for vedolizumab and infliximab, four for adalimumab), dividing by the number of weeks between maintenance treatments (eight for vedolizumab and infliximab, two for standard adalimumab, and one for escalated adalimumab), multiplying by the number of units per dose (one for vedolizumab and adalimumab, four for standard infliximab, and seven for escalated infliximab), and finally adding in the number of units used in the induction phase (three for vedolizumab, 12 for infliximab, and six for adalimumab). The same calculation was used for year 2, with only the induction phase components removed.

The base-case analysis assumed that 100% of vedolizumab patients would use the dosing recommended in the product monograph:[2] 300 mg on weeks 0, 2, and 6, and then every eight weeks thereafter. In contrast, the manufacturer assumed that 16% of infliximab patients and 22.9% of adalimumab patients would escalate to higher doses after the initiation phase during year 1, and 32% of infliximab and 45.8% of adalimumab patients would be on the escalated dose in year 2, based on the manufacturer's interpretation of the number of patients escalating in the ACCENT I infliximab[3,4] and CLASSIC II adalimumab[5] trials. (See Table 3.)

**TABLE 3: SUMMARY OF MANUFACTURER'S BASE CASE DRUG ACQUISITION COSTS AND TREATMENT USE**

| Treatment | Unit Cost ($) | Dose[a] | No. Units Year 1[b] | No. Units Year 2[b] | Proportion of Patients per Dose[c] |
|---|---|---|---|---|---|
| Vedolizumab (Entyvio, 300 mg per vial) | 3,290.00 | 300 mg IV infusion weeks 0, 2, and 6, then every 8 weeks thereafter | 7.77 | 6.52 | 100% |
| Infliximab (Remicade, 100 mg per vial) | 987.56 | Standard Dose<br>5 mg/kg IV infusion weeks 0, 2, and 6, and every 8 weeks thereafter (70 kg patients assumed, 4 vials per treatment) | 31.09 | 26.09 | 84% year 1<br>68% year 2 |
| | | Escalated Dose<br>5 mg/kg IV infusion weeks 0, 2, and 6, increasing to 10 mg/kg every 8 weeks thereafter (70 kg patients assumed, 4 vials per induction treatment, 7 vials per treatment after induction) | 45.41 | 45.66 | 16% year 1<br>32% year 2 |
| Adalimumab (Humira, 40 mg per syringe) | 740.36 | Standard Dose<br>160 mg SC week 0, 80 mg week 2, and 40 mg every other week thereafter | 30.09 | 26.09 | 77.1% year 1<br>54.2% year 2 |
| | | Escalated Dose<br>160 mg SC week 0, 80 mg week 2, 40 mg weekly thereafter | 54.18 | 52.18 | 22.9% year 1<br>45.8% year 2 |

IV = intravenous; ODB = Ontario Drug Benefit; SC = subcutaneous.

[a] Dosing for vedolizumab, infliximab, and adalimumab taken from respective product monographs.[2,9,10] Excess infliximab in vials was assumed wasted.

[b] Calculated by dividing 365.25 days by 7 days per week, subtracting the length of the induction phase, and then dividing by the frequency of administration in weeks. E.g., vedolizumab year 1: {[(365.25/7 )–14]/8 + 3 induction doses} × 1 unit per dose = 7.77; vedolizumab year 2: 365.25/7/8 × 1 unit per dose = 6.52.

[c] Proportion of patients escalating dose derived using data from the ACCENT I trial for infliximab[3,4] and CLASSIC II trial for adalimumab.[5]

Source: Adapted from Tables 6-1 through 6-5 of manufacturer's pharmacoeconomic submission, as well as submitted model. Unit cost for Entyvio is the submitted and current market price, unit costs for Remicade and Humira are from the ODB Exceptional Access Program (January 2016).

Using the unit costs, the estimated number of units per regimen, and the proportions of patients escalating to the higher doses of infliximab and adalimumab assumed above (Table 3), the manufacturer concluded that two years of treatment with vedolizumab ($25,571 and $21,458 per patient in years 1 and 2, respectively) would cost less than adalimumab ($26,361 and $28,162 per patient in years 1 and 2, respectively) and infliximab ($32,965 and $31,948 per patient in years 1 and 2, respectively) (Table 4) .

**TABLE 4: MANUFACTURER'S BASE CASE TOTAL DRUG AND INCREMENTAL COSTS (SAVINGS) OF VEDOLIZUMAB VERSUS COMPARATORS**

| Treatment | Average Dose-Weighted Cost Year 1 ($) | Average Dose-Weighted Cost Year 2 ($) |
|---|---|---|
| Vedolizumab | 25,571 | 21,458 |
| Infliximab | 32,965 | 31,948 |
| Adalimumab | 26,361 | 28,162 |
| Incremental cost vedolizumab vs. infliximab | (7,394) | (10,490) |
| Incremental cost vedolizumab vs. adalimumab | (790) | (6,704) |

vs. = versus.
Source: Adapted from Table 7-1 of manufacturer's pharmacoeconomic submission.

The manufacturer also conducted a series of sensitivity analyses, exploring the impact of 47.2% of patients adding an extra vedolizumab dose at week 10, as well as varying the proportion of infliximab and adalimumab patients escalating to the higher recommended dosing schedule based on those found in the literature. None of these analyses had a substantial impact on the relative cost of comparators when compared with the base case.

## 2. CADTH Common Drug Review Results

In June of 2016, Inflectra (infliximab), a subsequent entry biologic (SEB) to Remicade, received a Notice of Compliance from Health Canada for the treatment of adult patients with moderately to severely active Crohn's disease.[8] Inflectra has a recommended dosing schedule that is identical to that of Remicade[9] and is reimbursed on the ODB Formulary at a price of $525.00 per 100 mg vial, although ODB limited-use criteria for Inflectra do not yet include Crohn's disease. Inflectra is currently under review by the CADTH Common Drug Review (CDR) for the treatment of Crohn's disease; assuming it is reimbursed for Crohn's disease by public drug plans, it will be an economic comparator of interest for vedolizumab and is thus included in all following CDR reanalyses.

CDR noted that the method of calculation employed by the manufacturer to determine the number of units used in year 1 was not consistent with the number of units that would be used by a patient in weeks 0 through 51 of therapy and that the number of units reported for year 2 was in fact the number of units that would represent an average maintenance year thereafter. The number of doses considered for CDR reanalyses represent the actual number of doses that would be needed for patients' treatment in practice.

CDR's reanalysis resulted in a year 1 cost of $26,320 per patient for vedolizumab at the monograph-recommended dose ("approved dose"), which is less than that of branded infliximab at standard ($31,602) or escalated doses ($46,415) as well as the escalated dose of adalimumab ($39,979), but more than either dose of SEB infliximab ($16,800 standard, $24,675 escalated) and standard-dose adalimumab ($22,211) (Table 5). Incremental costs in subsequent years follow similar patterns, with the exception of standard-dose vedolizumab ($21,458 per patient) being less expensive than escalated SEB infliximab ($23,970 per patient).

**TABLE 5: THE CADTH COMMON DRUG REVIEW'S UNITS, COSTS, AND INCREMENTAL COSTS FOR STANDARD AND ESCALATED DOSING, INCLUDING SUBSEQUENT ENTRY BIOLOGIC INFLIXIMAB**

| | | | Year 1 | | | | Average Subsequent Year | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment** | **Unit Cost[a]** | **Dose Schedule** | **No. Units Year 1[b]** | **Drug Cost Year 1** | **Inc. Cost (Savings) With Approved VDZ** | **% Reduction (Increase) for VDZ to Match Comparator Cost** | **No. Units Year 2[b]** | **Drug Cost Average After Year 1** | **Inc. Cost (Savings) With Approved VDZ** | **% Reduction (Increase) for VDZ to Match Comparator Cost** |
| Vedolizumab (Entyvio)[c] | $3,290.00 | Approved | 8 | $26,320 | Ref | Ref | 6.52 | $21,458 | Ref | Ref |
| Infliximab (Remicade) | $987.56 | Standard | 32 | $31,602 | ($5,282) | (20%) | 26.09 | $25,765 | ($4,306) | (20%) |
| | | Escalated | 47 | $46,415 | ($20,095) | (76%) | 45.66 | $45,088 | ($23,630) | (110%) |
| Infliximab (Inflectra) | $525.00 | Standard | 32 | $16,800 | $9,520 | 36% | 26.09 | $13,697 | $7,762 | 36% |
| | | Escalated | 47 | $24,675 | $1,645 | 6% | 45.66 | $23,970 | ($2,511) | (12%) |
| Adalimumab (Humira) | $740.36 | Standard | 30 | $22,211 | $4,109 | 16% | 26.09 | $19,315 | $2,143 | 10% |
| | | Escalated | 54 | $39,979 | ($13,659) | (52%) | 52.18 | $38,631 | ($17,172) | (80%) |

Inc. = incremental; ODB = Ontario Drug Benefit; Ref = reference; VDZ = vedolizumab.

[a] Unit cost for Entyvio is the submitted and current market price; unit costs for Remicade and Humira are from the ODB Formulary Exceptional Access Program (July 2016). Infliximab dose based on a 70 kg patient.

[b] Doses counted from weeks 0 through 51 of treatment for year 1 and based on a 365.25-day year for average subsequent maintenance year.

[c] Vedolizumab is assumed to be at the approved dose and does not reflect escalated doses that may be used in clinical practice.

Using the proportions of patients escalating doses assumed by the manufacturer in its base case and assuming that SEB infliximab has the same proportion as branded infliximab, the year 1 cost of approved-dose vedolizumab ($26,320 per patient) is $7,652 less than the dose-weighted average cost of branded infliximab ($33,972 per patient), but $40 more than that of adalimumab ($26,280 per patient), and $8,260 more than that of Inflectra-brand infliximab ($18,060). The average cost of approved-dose vedolizumab in subsequent years ($21,458 per patient) was $10,490 less than the dose-weighted average cost of branded infliximab ($31,948 per patient), and $6,704 less than that of adalimumab ($28,162 per patient), but $4,474 more than that of SEB infliximab ($16,984 per patient) (Table 6).

**TABLE 6: THE CADTH COMMON DRUG REVIEW'S REANALYSIS DOSE-WEIGHTED AVERAGE COSTS AND INCREMENTAL COSTS (SAVINGS) OF VEDOLIZUMAB VERSUS COMPARATORS**

| Treatment | Escalated Dose Proportion[a] | Average Dose-Weighted Cost Year 1 | Average Dose-Weighted Cost Subsequent Years |
|---|---|---|---|
| Vedolizumab (Entyvio) | 0% | $26,320 | $21,458 |
| Infliximab (Remicade) | Year 1: 16.0%<br>Year 2: 32.0% | $33,972 | $31,948 |
| Infliximab (Inflectra) | Year 1: 16.0%<br>Year 2: 32.0% | $18,060 | $16,984 |
| Adalimumab (Humira) | Year 1: 22.9%<br>Year 2: 45.8% | $26,280 | $28,162 |
| **Incremental cost vedolizumab vs. infliximab (Remicade)** | | ($7,652) | ($10,490) |
| **Incremental cost vedolizumab vs. infliximab (Inflectra)** | | $8,260 | $4,474 |
| **Incremental cost vedolizumab vs. adalimumab** | | $40 | ($6,704) |

vs. = versus.
[a] Proportion of patients escalating dose was assumed the same as in the manufacturer's submission (see Table 3). Inflectra proportions assumed the same as Remicade-brand infliximab. Infliximab dose based on a 70 kg patient.

The escalation rate of 32% at the start of year 2 derived by the manufacturer for infliximab from the ACCENT I trial appears higher than those rates reported in two observational studies. One reported an escalation rate of 1.4% per patient-month (roughly 31% at the *end* of year 2) for infliximab patients on 5 mg/kg who had received at least one maintenance dose,[15] while the other reported 55.7 months as the bottom of the interquartile range for time to secondary loss of response, and thus slightly less than 25% of patients had experienced secondary loss of response and dose escalation by the end of year 1.[16] It is worth noting that neither of these studies specified that escalation needed to be to 10 mg/kg every eight weeks.

CDR conducted a sensitivity analysis in which 2.8% of infliximab patients were assumed to escalate to the 10 mg/kg dose every eight weeks after the induction period, to reflect the 1.4% per patient-month dose-escalation rate for infliximab patients with Crohn's disease estimated in the first observational study above.[15] The dose-weighted average year 1 cost of branded infliximab was $32,431 per patient using this method, while that of SEB infliximab was $17,241.

However, the statistics used by the manufacturer to estimate the proportion of patients who would escalate, along with the timing of those escalations, are not comparable between drugs:

- **Infliximab 32%** represents 181 ACCENT I patients who had initially responded to infliximab at week 2 and were randomized to 5 mg/kg of infliximab every eight weeks after induction, but who escalated to 10 mg/kg by week 54 (58 of 181 = 32%). Of note, only 36 of these 58 patients (62%) continued therapy to week 54.[3]
- **Adalimumab 45.8%** represents 204 CLASSIC II patients who were not in remission at weeks 0 and 4 and moved to a 40 mg adalimumab biweekly open-label cohort. 131 of 204 patients completed 56 weeks of treatment, 60 of whom had been escalated to 40 mg adalimumab weekly (60 of 131 = 45.8%).[5]
- **Vedolizumab 47.2% in sensitivity analysis** represents the 412 of 873 GEMINI II patients who had not achieved clinical response by week 6 and who were then assigned to 300 mg vedolizumab every four weeks (412 of 873 = 47.2%), and not to a single additional dose at week 10 as assumed in the manufacturer's sensitivity analysis. Of note, only 69 of these 412 patients continued therapy to week 52 (17%), most due to lack of efficacy.[7]

These differences make it unlikely that the proportions of patients the manufacturer assumed would escalate to and remain on higher doses on each drug are comparable or reflect clinical practice. Of particular importance, the absence of a recommended dose escalation in the vedolizumab product monograph[2] does not imply that the approved-dose vedolizumab is equally effective to escalated doses or a proportional mix of patients on standard and escalated doses of either infliximab or adalimumab; the manufacturer's submitted indirect treatment comparison was conducted using standard-dose trial data for each comparator (see CDR Clinical Report, Appendix 6), and thus any assumption of clinical similarity, uncertain as it may be, should also be based on the standard-dose schedules.

The clinical expert consulted by CDR believed it highly probable that vedolizumab patients with a secondary loss of response would be escalated to treatment every four weeks as per the higher-exposure arm in the GEMINI II trial[6] as well as those patients who had not adequately responded by week 6 in GEMINI II, despite this dosing schedule (and that assumed in the manufacturer's sensitivity analysis) not being included in the Health Canada–approved product monograph.[2]

CDR conducted an exploratory analysis assuming a varying proportion of patients escalating to the higher dosing regimen for each comparator (Table 7). Prices can then be compared at differing escalation rates under varying scenarios or as data become available. For example, if 30% of infliximab patients are using 10 mg/kg every eight weeks, while 50% of adalimumab patients are using 40 mg weekly and 50% of vedolizumab patients are using 300 mg every four weeks (i.e., escalation proportions similar to those cited by the manufacturer), then the average annual cost of maintenance vedolizumab ($32,194 per patient) is $632 more than that of branded infliximab ($61,562 per patient), $3,221 more than that of adalimumab ($28,973 per patient), and $15,416 more than that of SEB infliximab ($16,779 per patient).

**TABLE 7: THE CADTH COMMON DRUG REVIEW'S EXPLORATORY ANALYSIS VARYING PROPORTION OF PATIENTS ESCALATING ACROSS ALL COMPARATORS**

| Drug | Average Annual Maintenance Cost by Proportion of Patients on Escalated Dose of Each Comparator | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0% | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100% |
| **Vedolizumab**[a] | $21,458 | $23,606 | $25,753 | $27,900 | $30,047 | $32,194 | $34,341 | $36,488 | $38,636 | $40,783 | $42,930 |
| **Infliximab (Remicade)**[b] | $25,765 | $27,697 | $29,629 | $31,562 | $33,494 | $35,427 | $37,359 | $39,291 | $41,224 | $43,156 | $45,088 |
| **Infliximab (Inflectra)**[b] | $13,697 | $14,724 | $15,751 | $16,779 | $17,806 | $18,833 | $19,860 | $20,888 | $21,915 | $22,942 | $23,970 |
| **Adalimumab (Humira)**[c] | $19,315 | $21,247 | $23,179 | $25,110 | $27,042 | $28,973 | $30,905 | $32,836 | $34,768 | $36,699 | $38,631 |

[a] Proportion of patients who have escalated to 300 mg vedolizumab every 4 weeks.
[b] Proportion of patients who have escalated to 10 mg/kg. Infliximab dose based on a 70 kg patient.
[c] Proportion of patients who have escalated to 40 mg weekly.

It is important to note that the analyses conducted by both the manufacturer and CDR fail to account for the relative likelihood of patients discontinuing therapy on any given comparator, and who thus stop accruing both costs and benefits during the two-year time horizon, as well as patients who switch treatments. CDR estimated cost per patient and cost per completer analyses after one year of therapy for all comparators, but concluded that there were too many differences in trial design, patient characteristics, and reported information regarding timing of discontinuation between ACCENT I, CLASSIC II, and GEMINI II for the results to be appropriately compared.

Finally, the clinical expert consulted by CDR emphasized that a variety of escalation regimens are used in Canadian clinical practice rather than only those specified in the manufacturer's submission or the product monographs. For example, infliximab may be increased to 5 mg/kg every six weeks before escalation to 10 mg/kg dosing is attempted based on individual patient response. The expert believed it likely that escalation of vedolizumab based on patient response would eventually follow similar patterns once clinicians became familiar with its use.

# REFERENCES


1. Canadian Drug Expert Committee final recommendation: vedolizumab (Entyvio - Takeda Canada Inc.). Indication: ulcerative colitis [Internet]. Ottawa: CADTH; 2015 Oct 28. [cited 2016 May 12]. (Common Drug Review). Available from: https://www.cadth.ca/sites/default/files/cdr/complete/SR0421_cdr_complete_Entyvio_Nov-2-15_e.pdf
2. Entyvio™ (vedolizumab) powder for concentrate for solution in infusion 300 mg/vial [product monograph]. Oakville (ON): Takeda Canada; 2016 Mar 22.
3. Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology. 2004 Feb;126(2):402-13.
4. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002 May 4;359(9317):1541-9.
5. Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut [Internet]. 2007 Sep [cited 2016 May 17];56(9):1232-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2701613
6. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013 Aug 22;369(8):711-21.
7. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease [supplementary appendix]. N Engl J Med. 2013 Aug 22;369(8):711-21.
8. [Pr]Inflectra™ (infliximab): powder for solution, sterile, lyophilized, 100 mg/vial [product monograph]. Incheon, South Korea: Celltrion Healthcare Ltd.; 2016 Jun 10.
9. [Pr]Remicade® (infliximab): powder for solution, sterile, lyophilized, 100 mg/vial [product monograph]. Toronto: Janssen Inc.; 2016 Apr 26.
10. [Pr]Humira® (adalimumab): 40 mg in 0.8 mL sterile solution (50 mg/mL) subcutaneous injection [product monograph]. St. Laurent (QC): AbbVie Corporation; 2016 Apr 6.
11. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy. Final appraisal determination [Internet]. London: National Institute for Health and Care Excellence (NICE); 2015. [cited 2016 May 12]. Available from: https://www.nice.org.uk/guidance/TA352/documents/crohns-disease-moderate-to-severe-vedolizumab-final-appraisal-determination-document2
12. 10-year currency converter [Internet]. Ottawa: Bank of Canada; 2016. [cited 2016 Jul 22]. Available from: http://www.bankofcanada.ca/rates/exchange/10-year-converter/
13. Vedolizumab 300mg powder for concentrate for solution for infusion (Entyvio®). Takeda UK Ltd [Internet]. Glasgow (UK): Scottish Medicines Consortium; 2015 Jun 5. [cited 2016 May 12]. Available from: https://www.scottishmedicines.org.uk/files/advice/vedolizumab_Entyvio_FINAL_June_2015_for_website.pdf

14. Pharmaceutical Benefits Advisory Committee. Vedolizumab, 300mg vial; Entyvio®; Takeda Pharmaceuticals Australia [Internet]. Canberra: Australian Government; 2015. March 2015 PBAC meeting. [cited 2016 May 12]. (Public summary document). Available from: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-03/Files/vedolizumab-1-psd-march-2015.docx

15. Taxonera C, Olivares D, Mendoza JL, Diaz-Rubio M, Rey E. Need for infliximab dose intensification in Crohn's disease and ulcerative colitis. World J Gastroenterol [Internet]. 2014 Jul 21 [cited 2016 Jul 11];20(27):9170-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4112868/pdf/WJG-20-9170.pdf

16. Ma C, Huang V, Fedorak DK, Kroeker KI, Dieleman LA, Halloran BP, et al. Crohn's disease outpatients treated with adalimumab have an earlier secondary loss of response and requirement for dose escalation compared to infliximab: a real life cohort study. J Crohns Colitis [Internet]. 2014 Nov [cited 2016 Jul 11];8(11):1454-63. Available from: http://ecco-jcc.oxfordjournals.org/content/eccojc/8/11/1454.full.pdf